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Total Number of Pages in This Submission	9

Application Number	09/806,370
Filing Date	10/3/2001
First Named Inventor	Holmes
Art Unit	1645
Examiner Name	V. Portner
Attorney Docket Number	33,383-00

ENCLOSURES (Check all that apply)

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- ☐ Amendment/Reply
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Date	March 16, 2007	Reg. No.	31,215

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. : 09/806,370 Confirmation No.: 8568

Appellant : Holmes et al.

Filed : October 3, 2001

TC/A.U. : 1645

Examiner : V. Portner

Docket No. : 33,383-00

Customer No. : 38199

Title : MUTANT CHOLERA HOLOTOXIN AS AN ADJUVANT

Mail Stop Appeal Brief - Patents
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REPLY BRIEF

Sir:

This Reply Brief is timely filed in response to the Examiner's Answer mailed January 17, 2007.

No fee is believed due in connection with this paper. However, the Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

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I. Status of claims

The pending claims are 1-11, 13-17, 28-37, and 39-44. Claims 1-2 and 13 remain rejected following the Examiner's Answer. Claims 3, 43 and 44 are allowed. Claims 4-11, 14-17, 28-37 and 39-42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-2 and 13 are now the subject of this appeal.

II. Summary of claimed subject matter

Appellants' invention as presented in claim 1 is drawn to an antigenic composition that includes at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite (page 9, lines 20-25 and original claim 1). The composition also includes an effective adjuvanting amount of a mutant cholera holotoxin (page 9, line 25-26 and original claim 1). The mutant holotoxin has reduced toxicity compared to a wild-type cholera holotoxin (page 9, lines 26-27 and original claim 1) and has an amino acid (other than aspartic acid (Asp)) which replaces the deleted glutamic acid (Glu) which naturally occurs at position 29 of the mature A subunit of the wild-type cholera holotoxin (page 9, lines 28-30 and original claim 1). The mutant holotoxin enhances the immune response in a vertebrate host to the antigen (page 9, lines 20-22).

III. Grounds of rejection to be reviewed on appeal

The issue remaining on appeal is the following:

whether the examiner's rejection of claims 1, 2, and 13 under the provision of 35 USC § 102(b) over Glineur et al., Infection and Immunity, 62(10):4176, 1994 (hereinafter Glineur) should be reversed.

IV. Argument

Claims 1-2 and 13 are rejected under 35 USC § 102(b) over Glineur et al., Infection and Immunity, 62(10):4176 (1994, hereinafter "Glineur").

The Examiner asserts that Glineur discloses

> "a composition comprising a mutant holotoxin with reduced toxicity (see Table 1, page 4181) cholera in combination with additional antigens, specifically a 27 and 12 kDA antigen (see page 4180, column 1, Figure 4, page 4181, lane labeled "E29Δ"), all of the antigens produced by the recombinant host cell *Vibrio cholerae* 569-B-NT upon expression, as well as the expressed ampicillin resistance antigen (see Figure 3, "amp", "CTA", "CTB" and page 4180, column 2, paragraph 1), wherein the mutant cholera holotoxin was mutated through deleting the native Glu at position 29, and replacing the deleted Glutamic acid with an amino acid that is neither glutamic acid or aspartic acid (see Figure 2, frame B, line labeled CTX1 E29Δ), wherein the amino acid that replaced the native position 29 Glutamic acid was tyrosine." Page 4, para 9 of the Examiner's Answer.

Appellants respectfully request reconsideration and withdrawal of this rejection in view of the following remarks.

As required by MPEP § 2131, in order for Glineur to be a proper 35 USC § 102(b) reference, Glineur must teach ***every element*** of the claims. However, Glineur does not teach the claims of this application because Glineur does not teach:

- the mutant cholera holotoxin described in Appellants' claims; and
- any antigenic composition in which a mutant cholera holotoxin, and specifically the mutant cholera holotoxin described in Appellants' claims, is used as an adjuvant for another antigen.

Glineur Does Not Teach the Mutant Cholera Holotoxin Mutant Described in Appellants' Claims

Glineur's teachings related to cholera toxin mutants are limited to two mutant cholera holotoxins: (1) the deletion mutant E29Δ and (2) the substitution mutant E29D. Clearly, the second mutant is explicitly excluded from Appellants' claims.

Glineur's E29Δ deletion mutant is **not** the same as the mutant holotoxin component of Appellants' claims to an antigenic composition. In the E29Δ mutant, the wildtype Glu29 is deleted and no other amino acid is inserted in its place. Rather, the remaining amino acids of the holotoxin are shifted to other positions in the sequence. Glineur does not teach in E29Δ that the Glu that naturally occurs in wild-type cholera holotoxin at position 29 could be replaced with an amino acid other than Asp or that the same would provide a cholera toxin mutant with the properties necessary (including reduced toxicity) for use as an adjuvant in an antigenic composition. It is only Appellants' disclosure that provides the teaching and support for successful use of an amino acid **substitution *other than Asp*** at wildtype position E29 to create a mutant cholera holotoxin useful as an adjuvant in an antigenic composition.

Glineur in no way teaches the requirements of the mutant cholera holotoxin of the antigenic composition of the pending claims. Glineur necessarily fails to teach a recited element in the claim, namely a naturally occurring Glu at position 29, which is in turn substituted by an amino acid other than Asp. Thus, Glineur does not anticipate the mutant cholera holotoxin which is a component of the claimed antigenic composition of the amended claims.

Glineur Does Not Teach an Antigenic Composition in which a Mutant Cholera Holotoxin is used as an Adjuvant for Another Antigen

Despite the Examiner's characterization of Glineur at page 4179-4181 and Figs. 2-4 of Glineur cited above, Glineur does not teach the antigenic composition of

Appellants in which a mutant cholera holotoxin is used an an adjuvant for another antigen. Specifically Fig. 2 at page 4179 simply shows the constructs of the two E29D and E29Δ mutants. The paragraph starting on col. 2, describes the *V. cholerae* expression system for these mutants. The 27 kDA and 12 kDA "antigens" so characterized by the examiner are simply anti-CTX-reactive polypeptides detected in the purified toxin preparations (page 4179, col. 2, last 4 lines through page 4180, col. 1; also Fig. 4). One polypeptide is considered to be an unnicked form of cholera holotoxin subunit A (CTA) and the other is theorized to be a modified form of cholera holotoxin subunit B (CTA) or a proteolytic fragment of CTA. These polypeptides are **not** recited to be antigens to be adjuvanted by the mutant cholera toxin in question. These polypeptides in combination with the mutant cholera holotoxin E29Δ have absolutely nothing to do with the antigenic composition of Appellants' claims and are not any anticipation of Appellants' claims.

Glineur clearly does not teach an antigenic composition which contains a first antigen and a mutant cholera holotoxin (CTX) that has an "adjuvant" effect on the first antigen.

In fact, contrary to the Examiner's argument at page 6, paragraph "3." of the Examiner's Answer, the E29D mutant described in Glineur "...had no significant effect on the ADP-ribosyltransferase activity"[1] and consequently would not be useful as an adjuvant, because it had the enzymatic activity of the wild-type CTX. The E29Δ mutant, which contained a simple deletion of position 29, instead of a substitution, was indicated to diminish the enzymatic activity of the holotoxin. This pair of conclusions would lead one of skill in the art to assume that the replacement of the wildtype Glu 29 with another amino acid, as opposed to its deletion without replacement, would **not** reduce the enzymatic activity of the holotoxin. The fact remains that Glineur does not anticipate the antigenic composition of Appellants' claims. Even if the Examiner were to raise an argument under 35 USC § 103, these

[1] Page 4181, col. 2 and Table 1 of Glineur

inconsistent "suggestions" of Glineur teach away from Appellants' claims, which is evidence of nonobviousness.

In view of the above remarks, this rejection should be withdrawn.

Reversal of the examiner's rejection of the claims under appeal (claims 1-11 and 13) is respectfully requested.

Respectfully submitted,

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